REMARKS

Status of the Claims

Claims 20, 21, 83-87, 97-107, 109-118, 128-138 and 140-149 were pending in the present application. Claims 108 and 139 were withdrawn from consideration, and claims 20, 21, 83-87, 97-107, 109-118, 128-138, and 140-149 were rejected. By virtue of this response, claims 83-86, 97, 100-105, 114-117, 131-136, 148, and 149 have been cancelled, claims 20, 21, 87, 98, 106, 118, 128, 137, and 144 have been amended, and new claims 150-189 have been added. Accordingly, claims 20, 21, 87, 98-99, 106, 107, 109-113, 118, 128-130, 137, 138, 140-147 and 150-189 are currently under consideration.

With respect to all amendments and cancelled claims, Applicants have not dedicated or abandoned any unclaimed subject matter and, moreover, have not acquiesced to any rejections and/or objections made by the Office. Applicants reserve the right to pursue prosecution of any presently excluded claim embodiments in future continuation, continuation-in-part and/or divisional applications.

Amendments to the Claims

Claims 83-86, 97, 100-105, 114-117, 131-136, 148, and 149 have been cancelled, claims 20, 21, 87, 98, 106, 118, 128, 137, and 144 have been amended, and new claims 150-189 have been added. No new matter is added.

Independent claim 20, as amended, is directed to a method of preventing or treating a disease in a host, comprising administering to the host an effective amount of a vaccine comprising a modified *Listeria monocytogenes* bacterium, wherein the nucleic acid of the modified bacterium comprises psoralen adducts that attenuate the modified bacterium for proliferation relative to the bacterium without the adducts, wherein the bacterium further comprises a genetic mutation that attenuates the ability of the bacterium to repair its modified nucleic acid relative to wild type.

Support for the amendment of claim 20 is found, e.g., in paragraphs [0115], [0122], [0079], [0100], and [0114] as well as elsewhere in the application as filed.

Independent claim 21, as amended, is directed to a method of inducing an immune response in a host to an antigen comprising administering to the host an effective amount of a vaccine comprising a modified *Listeria monocytogenes* bacterium, wherein the nucleic acid of the modified bacterium comprises psoralen adducts that attenuate the modified bacterium for proliferation relative to the bacterium without the adducts, and wherein the modified bacterium expresses the antigen. Support for the amendment of claim 21 is found, e.g., in paragraphs [0115], [0122], [0079], and [0100], as well as elsewhere in the application as filed.

Claims 87 and 118 are amended to recite that the nucleic acid of the modified bacterium has been modified by reaction with 4'-(4-amino-2-oxa)butyl-4,5',8-trimethylpsoralen activated by irradiation. Support is found throughout the application as filed, e.g., in paragraphs [0100], [0006], and [0029].

Claim 128 was amended to add the term "further" to clarify that the genetic mutation is in addition to elements articulated in claim 21.

Claim 144 has been amended to add "survivin" and "mcm-2" to the list of tumor antigens. Support for this amendment is found in paragraph [0102].

In addition, minor, conforming amendments are made to claims 98, 106, and 137.

New independent claim 152 is directed to a method of preventing or treating a disease in a host, comprising administering to the host an effective amount of a vaccine comprising a modified *Listeria monocytogenes* bacterium, wherein the modified bacterium comprises nucleic acid crosslinks that attenuate the modified bacterium for proliferation relative to the bacterium without the crosslinks, and wherein the bacterium further comprises a genetic mutation that attenuates the

ability of the bacterium to repair its nucleic acid that has been modified relative to wild type. Support for this claim is found through the application as filed, including, e.g., in paragraphs [0029], [0100], [0115], [0122], [0006], and [0015].

New independent claim 168 is directed to a method of inducing an immune response in a host to an antigen comprising administering to the host an effective amount of a vaccine comprising a modified *Listeria monocytogenes* bacterium, wherein the modified bacterium comprises nucleic acid crosslinks that attenuate the modified bacterium for proliferation relative to the bacterium without the crosslinks and wherein the modified bacterium expresses the antigen. Support for this claim is found through the application as filed, including, e.g., in paragraphs [0029], [0100], [0115], [0122], [0006], and [0015].

Support for new dependent claims 150, 151, 153-167, and 169-189 is found throughout the application as filed and as indicated in the following table:

NEW CLAIM NO(S).	EXEMPLARY SUPPORT IN SPECIFICATION AND/OR ORIGINAL CLAIMS
150, 151	Paragraphs [0100], [0115], [0120], and [0229]
153, 169	Paragraphs [0006] and [0124]
154, 155, 170, 171	Paragraphs [0006], [0099], and [0029]
156-158, 172-174, 188-189	Paragraphs [0006], [0100] and [0029]
175	Paragraph [0006]
159-162, 176-179	Paragraphs [0114], [0015], [0117]-[0119], and [0028]
163, 180	Paragraph [0113]
164, 181-186	Paragraphs [0006], [0101]-[0108]
165, 187	Paragraphs [0006] and [0091]
166, 167	Paragraphs [0101] and [0132]
188, 189	Paragraphs [0006], [0029], and [0100]

Supplemental Information Disclosure Statements

The Examiner has alleged that the Information Disclosure Statement filed July 26, 2007, failed to comply with 37 CFR 1.98(a)(2) and has therefore not considered any of the foreign patent documents or non-patent literature submitted therewith.

Applicants contend that the Information Disclosure Statement filed July 26, 2007 was properly submitted. Applicants believe that copies of each of the foreign patent documents and non-patent literature listed on the PTO/SB/08 form enclosed with the Supplemental Information Disclosure Statement filed July 26, 2007 were submitted to the Office. Enclosed herewith is a copy of the date-stamped postcard received back from the Office acknowledging receipt of the documents filed July 26, 2007. The date-stamped postcard indicates that 117 references submitted with the Supplemental Information Disclosure Statement, were received by the Office. In addition, Applicants note that copies of numerous references submitted on July 26, 2007 appear to be showing on PAIR as of April 12, 2008.

Accordingly, Applicants respectfully request that all documents submitted with the Supplemental Information Disclosure Statement filed July 26, 2007, be considered and made of record.

An additional Supplemental Information Disclosure Statement has also been filed herewith. Consideration of these additional references is also requested.

Double Patenting Rejection

Claims 20-21, 83-87, 97-107, 109-118, 128-130, 131-138 and 139-149 were provisionally rejected on the ground of nonstatutory obviousness-type double patenting for allegedly being unpatentable over claims 32, 33, 60, 66, 90, 101 and 103 of copending Application No. 11/173,770. Applicants note that 32, 33, 60, 66, 90, 101 and 103 of copending Application No. 11/173,770 have been cancelled. Accordingly, withdrawal of the rejection is respectfully requested.

Claims Rejections under 35 U.S.C. § 112 – 2nd Paragraph

Claims 20, 21, 83-87, 97-107, 109-118, 128-138 and 140-149 were rejected under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner alleged that independent claims 20 and 21 were "vague and confusing" because the claims state "modified by reaction with a nucleic acid targeted compound that reacts directly with the nucleic acid so that the bacterium is attenuated for proliferation relative to the bacterium prior to modification, wherein gene expression in the modified bacterium is active."

Applicants respectfully traverse.

Since claims 83-86, 97, 100-105, 114-117, 131-136, 148, and 149 are cancelled by virtue of this Amendment, the rejection of those claims is moot.

Without acquiescing as to the merits of the rejection and solely in the interest of expediting prosecution, Applicants have amended claims 20 and 21. Claims 20 and 21, as amended, no longer recite "modified by reaction with a nucleic acid targeted compound that reacts directly with the nucleic acid so that the bacterium is attenuated for proliferation relative to the bacterium prior to modification, wherein gene expression in the modified bacterium is active."

In light of the foregoing, Applicants respectfully request that the rejection under 35 U.S.C. § 112, second paragraph, be withdrawn.

Claim Rejections under 35 U.S.C. § 112 – Scope of Enablement

Claims 20, 21, 83-92, 95-107, 109-123, 127-138 and 140-149 were rejected under 35 U.S.C. § 112, first paragraph, because the specification allegedly does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Applicants respectfully traverse.

Since claims 83-86, 97, 100-105, 114-117, 131-136, 148, and 149 are cancelled by virtue of this Amendment, the rejection of those claims is moot.

As argued in the response filed July 26, 2007, Applicants maintain that the full scope of the claims prior to the present amendment is fully enabled. Nevertheless, solely in order to expedite prosecution, and without acquiescing as to the merits of the rejection, independent claims 20 and 21 have both now been amended to recite "*Listeria monocytogenes* bacterium" instead of "bacterium." Additionally, again solely in order to expedite prosecution, and without acquiescing as to the merits of the rejection, independent claims 20 and 21 claims have now both been amended to no longer recite "nucleic acid targeted compound." Claims 20 and 21, as amended recite "the nucleic acid of the modified bacterium comprises psoralen adducts that attenuate the modified bacterium for proliferation."

The Examiner states on page 11 of the Office Action, "The specification does not provide evidence that one skilled in the art would know what modifications, and what regions of uvrA and uvrB to target for modifications, in order to produce an attenuated bacterium with the desired phenotype." Applicants disagree and contend that adequate direction and guidance *is* provided in Applicants' specification to enable one of ordinary skill in the art to make and/or use the full scope of the claimed invention, including a wide, representative variety of *uvrA* and *uvrB* mutations, as well as mutations in other known genes such as *uvrC*, *uvrD*, and/or *recA* that would attenuate the ability of the bacterium to repair its modified nucleic acid relative to wild type.

The enablement requirement of 35 U.S.C. § 112, paragraph 1, requires that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands,* 858 F. 2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988). The test of enablement is not whether any experimentation is necessary but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976). Furthermore, as stated in MPEP §2164.01, "A patent need not teach, and preferably omits, what is well known in the art. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir.

1986), cert. denied, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984)."

Listeria may be attenuated for the ability to repair nucleic acid by various routes that are readily attainable by one of ordinary skill in the art without any undue experimentation. It is significant that if a *uvrA* or *uvrB* mutant is generated such that the bacteria are attenuated for repair of nucleic acid, the expression and/or activity of the gene product is being *disrupted* by the mutation(s). Although it may be more of a challenge to identify mutant forms of a protein that maintain function or have improved function, that is not what is required here. Generating functional mutants of a protein can be difficult precisely because it is so easy to render a protein nonfunctional once the sequence is known, even if structural information about the protein is not known. For instance, a frame-shift mutation is going to disrupt any protein's function, regardless of whether or not the structure-function relationship of the protein is known. Likewise, it is generally routine for one skilled in the art to eliminate expression of the protein once the gene sequence has been identified. One of ordinary skill in the art would be readily able to generate, for example, mutants in which a significant part or all of the *uvrA* gene was deleted, mutants in which a stop codon had been placed early in the *uvrA* coding sequence, or mutants in which a insertion mutation causes a frame shift in the *uvrA* coding sequence. Even many of the possible point mutations that could be generated would be expected to disrupt the production of UvrA and/or UvrB, regardless of the specifics of the structure of these proteins. With respect to point mutations, Griffiths et al. states that, "it is always true that such mutations are more likely to reduce or eliminate gene function (thus they are loss-of-function mutations) than to enhance it. The reason is simple: it is much easier to break a machine than to alter the way that it works by randomly changing or removing one of its components." (page 315; Griffiths, et al. (2002) Modern Genetic Analysis, W.H. Freeman and Co., New York, NY).

In addition, confirming that any given mutation did in fact have the desired effect on the ability of the *Listeria* to repair its nucleic acid or screening for mutations that have the desired effect would be routine to one skilled in the art. For example, the attenuation of a mutant *Listeria* for its ability to repair its modified nucleic acid could easily be evaluated by those of ordinary skill in the

art by testing for an increased sensitivity to photochemical inactivation compared to the parent, unmodified *Listeria*.

Applicants respectfully submit that in light of Applicants' teachings and the knowledge of those of ordinary skill in the art, it would be routine for one of ordinary skill in the art to follow the guidelines set out in Applicants' specification to generate a representative number of appropriate *uvrA, uvrB, uvrC, uvrD*, and/or *recA* mutants in *Listeria*.

Applicants furthercontend that the claims directed to methods of prevention and treatment of disease are enabled for the full scope of the claims. Applicants have demonstrated with *in vivo* experiments that *Listeria* which have been attenuated for proliferation by treatment with a psoralen activated by UV irradiation are effective as immunotherapeutics against viral disease, bacterial disease, and cancer.

Evidence that the *Listeria* which have been treated with a UV-activated psoralen are capable of protecting mice against subsequent challenge with wild type *Listeria*, is provided, e.g., in Example 13 of the specification and in Figures 14, 15, and 16. See also Figure 5 and the discussion of results under the heading "S-59/UVA *LM* Δ*uvrAB* protects against bacterial challenge" in Brockstedt et al., Nat Med. 11(8):853-60 (2005) (cite no. 17 of the Supplemental Information Disclosure Statement filed April 10, 2006).

In addition, evidence that the *Listeria* which have been treated with the UV-activated psoralen can be efficacious against tumors is provided, e.g., in Example 15 and in Figure 19 of the application. In addition, results indicating that the modified *Listeria* are capable of breaking tolerance in mice, resulting in significantly reduced lung metastases and extended survival is provided, e.g., in Example 16 and in Figure 20 of the application. See also Figure 4 and the discussion of results under the heading "S-59/UVA *LM* Δ*uvrAB* therapeutic antitumor efficacy" in Brockstedt et al. (2005).

Furthermore, evidence that modified *Listeria* are capable of protecting mice against subsequent challenge with recombinant vaccinia virus expressing the ovalbumin model antigen can

be found in Figure 3 and the discussion of results under the heading "S-59/UVA *LM ΔuvrAB* protects against viral challenge" in Brockstedt et al. (2005).

One skilled in the art will recognize that the above-indicated results not only provide evidence that *Listeria* treated with UV-activated psoralen are suitable for use in immunotherapeutics, but also that, collectively, the data suggest that *Listeria* crosslinked in a similar manner by other means would also be generally suitable for use as vaccine vectors for delivery of appropriate antigens to treat or prevent a wide variety of diseases.

Lastly, Applicants draw the following recent review articles to the Examiner's attention as support for the contention that attenuated forms of *Listeria monocytogenes*, in general, have now been recognized in the art to be promising antigen-delivery vectors for the treatment of and protection from a variety of diseases: Liu et al., "Listeria-Based Anti-Infective Vaccine Strategies," Recent Patents on Anti-Infective Drug Discovery, 1:2821-290 (2006); and Bruhn et al., "Listeria as a Vaccine Vector," Microbes and Infection, 9:1226-1235 (2007). Copies of these two review articles are included in the Supplemental Information Disclosure Statement filed herewith.

In light of the foregoing remarks, Applicants respectfully request that the rejection under 35 USC § 112, first paragraph, be withdrawn.

Claim Rejections under 35 U.S.C. § 112 – Written Description

Claims 20, 21, 83-92, 95-107, 109-123, 127-138 and 140-149 were rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the written description requirement.

Applicants respectfully traverse.

Since claims 83-86, 97, 100-105, 114-117, 131-136, 148, and 149 are cancelled by virtue of this Amendment, the rejection of those claims is moot.

As argued in the response filed July 26, 2007, Applicants maintain that the full scope of the claims prior to the present amendment is supported by the application. Nevertheless, solely in order

to expedite prosecution, and without acquiescing as to the merits of the rejection, independent claims 20 and 21 have both now been amended to recite "*Listeria monocytogenes* bacterium" instead of "bacterium."

The Examiner asserts in the Office Action mailed October 15, 2007 that the "specification does not provide evidence that one skilled in the art would know what modifications, and what regions of the uvr gene's coding regions to target for modifications, in order to produce an attenuated bacterium." See page 16 of the Office Action. The Examiner further asserts that "one skilled in the art would not be able to recognize from the current disclosure any substitutions, or other mutations (except, perhaps, deletion of the whole polynucleotide) that would result in a decreased gene product activity." See page 16 of the Office Action. The Examiner cites the reference, Bowie et al., in support of her assertions.

Applicants respectfully disagree with the Examiner's assertions and contend that the Bowie et al. reference does not support the Examiner's assertions. Furthermore, Applicants respectfully submit that the specification of the present application does provide a representative number of species regarding the types of mutations that is sufficient to support a genus claim. In light of the knowledge of those of skill in the art in this area, those of skill in the art would recognize from Applicants' specification that Applicants were, in fact, in possession of the full scope of the invention as claimed.

Applicants respectfully contend that, contrary to the assertions of the Examiner, the Bowie et al. reference is irrelevant to the present application. The Bowie et al. reference describes "how an analysis of allowed amino acid substitutions in proteins can be used to reduce the complexity of sequences and reveal important aspects of structure and function." See first paragraph on page 1306 of Bowie et al. The Examiner has pointed to nothing in the reference which would indicate that one of ordinary skill in the art would not readily envision multiple different ways that could be used to *disrupt* the expression or functionality of a given sequence. Even if it is true that one of ordinary skill in the art may often have trouble making amino acid substitutions in a particular protein sequence while still maintaining functionality, this is irrelevant to the present application.

Unpredictability in making amino acid substitutions in a protein in which the structure-function relationship is unclear does not translate into there being unpredictability in the ability to *disrupt* the expression or function of a sequence. Regardless of how mysterious the structure-function relationships are, it would be obvious to one of ordinary skill in the art that disruption of expression and/or function of a gene would most likely occur if certain things are done, such as, but not limited to, any of the following: (a) deletion of the entire coding sequence; (b) deletion of the majority of the coding sequence; (c) generation of one or more stop codons early in the coding sequence; (d) a deletion early in the coding sequence that generates a frame-shift mutation (e) an insertion early in the coding sequence that generates a frame-shift mutation; (f) deletion of the promoter or other key control sequence; and (g) deletion of both the promoter and the coding sequence of the gene. The effect of these types of mutations are far more predictable than the effect of the types of individual amino acid substitutions discussed in Bowie et al.

In addition, confirming that any given mutation did in fact have the desired effect on the ability of the *Listeria* to repair its nucleic acid or screening for mutations that have the desired effect would be routine to one skilled in the art. For example, the attenuation of a mutant *Listeria* for its ability to repair its modified nucleic acid could easily be evaluated by those of ordinary skill in the art by testing for an increased sensitivity to photochemical inactivation compared to the parent, unmodified *Listeria*.

Furthermore, even if single point mutations in a gene are being made, one skilled in the art would recognize that such mutations would be more likely to disrupt the function of the gene than not. As noted above, with respect to point mutations, Griffiths et al. states that, "it is always true that such mutations are more likely to reduce or eliminate gene function (thus they are loss-of-function mutations) than to enhance it. The reason is simple: it is much easier to break a machine than to alter the way that it works by randomly changing or removing one of its components." (page 315; Griffiths, et al. (2002) Modern Genetic Analysis, W.H. Freeman and Co., New York, NY).

As indicated in MPEP 2163(II)(A)(2), generally "there is an inverse correlation between the level of skill and knowledge in the art and the specificity of disclosure necessary to satisfy the

written description requirement. Information which is well known in the art need not be described in detail in the specification. See, e.g., *Hybritech, Inc. v. Monoclonal Antibodies, Inc.* 802 F.2d 1367, 1379-80, 231 USPQ 81, 90 (Fed. Cir. 1986)." Applicants respectfully contend one of ordinary skill in the art would have been readily able to identify a wide variety of mutations for disrupting either expression of any target genes such as *uvrA* or *uvrB* and/or the functionality of the products of such genes and would have recognized Applicants as being in possession of such mutations. Since alternative methods for disrupting the expression or function of such genes would have been so obvious to one of ordinary skill in the art, it is not necessary to recite all such possible mutations or even any particular in order to meet the written description requirement. Applicants contend that, especially in light of the ease with which one of ordinary skill in the art could disrupt a variety of known target gene sequences in *Listeria*, the disclosures in the application are more than adequate to provide a representative number of species and meet the written description requirement for the full scope of the pending claims.

In light of above remarks, Applicants respectfully request that the rejection under 35 U.S.C. § 112, first paragraph, be withdrawn.

Claim Rejections under 35 U.S.C. § 102

1. Agrewala et al. (US 2002/0136738 A1)

Claims 20, 21, 83, 85, 86, 100, 110, 111, 112, 114, 116, 117, 131 and 142 were rejected under 25 U.S.C. § 102(e) for allegedly being anticipated by Agrewala et al.

Applicants respectfully traverse.

Without acquiescing to the rejection and solely in the interest of expediting prosecution, Applicants have cancelled claims 83, 85, 86, 100, 114, 116, 117, and 131 and amended claims 20 and 21, without prejudice. The rejection is considered moot with respect to the cancelled claims, and Applicants will therefore focus only on points of distinction with respect to the remaining

claims, as amended, as well as the new claims. However, Applicants note that points of patentable distinction also apply with respect to the cancelled claims and the claims prior to amendment.

Applicants contend that Agrewala et al. does not anticipate independent claims 20 and 21, as amended, or new independent claims 152 and 168, because Agrewala et al. does not teach the use of *Listeria monocytogenes*.

In addition, Agrewala et al. does not anticipate independent claims 20 and 21, as amended, because Agrewala et al. does not teach methods involving the use of a bacterium, wherein the nucleic acid of the modified bacterium comprises psoralen adducts that attenuate the modified bacterium for proliferation.

Furthermore, Agrewala et al. also does not anticipate independent claim 20, as amended, or new independent claim 152 because Agrewala et al. does not teach the use of bacteria that comprise a genetic mutation that attenuates the ability of the bacteria to repair its nucleic acid.

In light of the foregoing, Applicants respectfully request that the rejection under 35 U.S.C. § 102(e) over Agrewala et al. be withdrawn and not be applied to the newly added and amended claims.

2. BASF AG (WO 89/09616)

Claims 20, 83, 85, 97, 110, 111 and 112 were rejected under 35 U.S.C. § 102(b) for allegedly being anticipated by BASF AG.

Applicants respectfully traverse.

Without acquiescing to the rejection and solely in the interest of expediting prosecution, Applicants have cancelled claims 83, 85, 97, and 110 and amended claim 20, without prejudice. The rejection is considered moot with respect to the cancelled claims, and Applicants will therefore focus only on point of distinction with respect to the remaining claims, as amended, as well as the

new claims. However, Applicants note that points of patentable distinction also apply with respect to the cancelled claims and the claims prior to amendment.

Applicants contend that BASF AG does not anticipate independent claims 20 or 21, as amended, or new independent claims 152 and 168, because BASF AG does not teach methods involving the use of *Listeria monocytogenes*.

In addition, BASF AG does not anticipate independent claims 20 and 21, as amended, because BASF AG does not teach methods involving the use of a bacterium, wherein the nucleic acid of the modified bacterium comprises psoralen adducts that attenuate the modified bacterium for proliferation.

Furthermore, BASF AG also does not anticipate independent claim 20, as amended, or new independent claim 152 because BASF AG does not teach the use of bacteria that comprise a genetic mutation that attenuates the ability of the bacteria to repair its nucleic acid.

In light of the foregoing, Applicants respectfully request that the rejection under 35 U.S.C. § 102(b), over BASF AG be withdrawn.

Claim Rejection under 35 U.S.C. § 103

Claims 20, 21, 83, 84, 97, 98, 99, 110, 111, 112, 114, 115, 116, 117, 128-130, 136, 140-142 and 145 were rejected under 35 U.S.C. § 103(a) for allegedly being unpatentable over AKZO (WO 02/40046) in view of Sander et al. (Infect. Immun. June 2001. 69(6): 3562-3568) and Ferguson et al. (Mutation Research. 1987. 184: 13-21).

Applicants respectfully traverse.

Without acquiescing to the rejection and solely in the interest of expediting prosecution, Applicants have cancelled claims 83, 84, 97, 114-117, and 136 and amended claims 20, 21, 98, and 128, without prejudice. The rejection is considered moot with respect to the cancelled claims, and Applicants will therefore focus only on point of distinction with respect to the remaining claims, as

amended, as well as the new claims. However, Applicants note that points of patentable distinction also apply with respect to the cancelled claims and the claims prior to amendment.

Applicants contend that the cited combination of references does not render independent claims 20 and 21, as amended, obvious because the cited combination of references does not teach or suggest the use of "a vaccine comprising a modified *Listeria monocytogenes* bacterium, wherein the nucleic acid of the modified bacterium comprises psoralen adducts that attenuate the modified bacterium." For instance, none of the cited references, alone or in combination, suggests the use of *Listeria monocytogenes* as a vaccine. Furthermore, none of the references, either alone or in combination, suggests the use of modified bacteria comprising psoralen adducts that attenuate the modified bacterium for proliferation.

Similarly, Applicants contend that the cited combination of references does not render new independent claims 152 and 168 obvious, e.g., because the cited combination of references does not teach or suggest the use of *Listeria monocytogenes* as a vaccine.

In light of the foregoing, Applicants respectfully request that the rejection under 35 U.S.C. § 103, over AKZO, in view of Sander et al. and Ferguson et al. be withdrawn.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 643032000100. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: April 15, 2008

Respectfully submitted,

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Atty Docket No.: 282172002800

Inventor: Thomas W. DUBENSKY, Jr. et al.

Application No.: 10/773,618 **Filing Date:** February 6, 2004

Title: MODIFIED FREE-LIVING MICROBES, VACCINE COMPOSITIONS AND METHODS OF USE THEREOF

Documents Filed:

- Transmittal (1 page)
- Fee Transmittal (PTO/SB/17) plus duplicate for fee processing (2 pages)
- Processing Fee Transmittal (PTO/SB/17i) (1 page)
- Extension of Time Request (1 page)
- Amendment in Response to Non-Final Office Action (42 pages)
- Request to Correct Inventorship Under 37 C.F.R. §1.48(b) (2 pages)
- Request for Corrected Filing Receipt (2 pages)
- Marked-Up Copy of Filing Receipt (2 pages)
- Supplemental Application Data Sheet (4 pages)
- Supplemental Information Disclosure Statement (3 pages)
- Form PTO/SB/08a/b + copy (12 pages)
- 117 References

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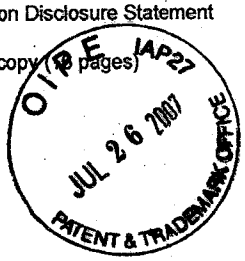

Via: Express Mail: Airbill No. EV 582594845 US

Sender's Initials: AJH4/say4 **Date:** July 26, 2007

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